Controversies and pitfalls in diagnosing Huntington's Disease

Valorisation

"Valorisation is the process of creating value from knowledge, by making this knowledge available and suitable for economic and social exploitation and to translate this knowledge into products, services, processes and new business" (1). With other words, a way in which one can express the importance of research by translating it into social, economic and financial value.

Introduction

Huntington's disease (HD) is a progressive, neurodegenerative disorder characterized by unwanted movements, psychiatric disorders, and cognitive deterioration. The disease is associated with a CAG repeat expansion in the Huntingtin (*HTT*) gene. Patients die in end stage disease approximately 20 years after the first onset of symptoms.

It is a rare disease with approximately 1,700 patients in the Netherlands. Because of the 50% chance of inheriting the disease if a parent has the disease, the estimation of persons at risk to develop HD is 6,000-9,000. Persons at risk can apply for predictive DNA testing to confirm or exclude if one is a Huntington's Disease Gene Expansion Carrier (HDGEC). HDGECs with 40 or more CAG repeats will develop disease nevertheless, 35 and below will not. Until now there is no cure or disease progression stabilising treatment.

The progressive and long-term nature of HD puts a substantial financial burden on patients, spouses and healthcare providers. Especially nursing home costs and job disqualification result in major financial burden. As would be expected with a degenerative condition, costs increase with disease severity. This thesis mainly focuses on the pitfalls in diagnosing HD for several groups of patients. For every group the final goal of the investigation was to undermine the pitfalls in diagnosis.

HD patients score statistically lower on health related Quality of Life (HrQoL) than mutation-negative controls across physical, emotional and social life domains (2). Reducing disease and psychological burden of patients and caregivers will eventually reduce healthcare costs as well. With disease progression the need for specialised care increases dramatically.

Societal impact of this thesis

In this thesis we investigated HD subgroups such as juvenile HD, late-onset, premanifest (carrier without symptoms) and carriers of an intermediate repeat. Furthermore the onset of disease was investigated.

The actual age of onset remains unclear in many patients. With numerous novel approaches for treatments in HD in development and several clinical trials that have been conducted

and further trials under way, it is very important to have accurate diagnostic criteria for age of onset. If disease modifying treatments become available, accurate defining onset of disease will not only contribute to earlier treatment possibilities, but also to more precise monitoring of treatment effects.

The aim of this thesis is to undermine the pitfalls in diagnosing HD subgroups such as late-onset and pediatric HD, and persons with an intermediate repeat size. In this way we hope to diminish the psychological burden for patients and their caregivers, the chance of misdiagnosis and/or delay of diagnosis.

Carriers with an intermediate allele (IA) are expected not to develop HD, although some case reports claim otherwise. Concluding that IAs are able to cause HD would have tremendous consequences in diagnosing and pre-symptomatic counselling HD. Not only would diagnostic protocols in HD counselling have to be adapted, it would also put an enormous psychological burden for carriers of an IA. As we were not able to confirm this with our investigation, we suppose this prevents unnecessary psychological burden for the group of IA carriers.

Defining the characteristics of groups such as late-onset and pediatric-onset will help physicians specialised in HD to give customised care and provide individualised information. This might also prevent health care professionals from unnecessary costly investigations and/or treatments.

It is yet unknown if persons at risk feel relieved when examination by a neurologist shows no signs of disease in that stage. Psychological burden of not knowing and the anxiety of having symptoms might be reduced by visiting a neurologist in the premanifest stage and therefore have a positive impact on optimising care as well as effectiveness in care for HD patients.

Conclusion

Fulfilling the needs of HD patients regardless the disease stage reduces burden as well as consumption of care. This thesis can help neurologists, genetics and psychiatrists to understand the needs of different groups of HD patients. If this is accomplished, quality of life of HD patients and their caregivers and family members will increase and health related costs will likely decline.

All HD patients will need extensive care at some time during their disease. However, if we want care to be provided efficiently, it is necessary to customise care regarding the stage of disease and group of patients (juvenile, late onset, intermediate). In this way patients and caregivers will get the best individual care and the total healthcare costs will be reduced as much as possible.

Furthermore, accurately defining onset of disease will contribute to start treatment possibilities as early as possible. Treatment costs will rise, but care costs will be postponed.

Reference List

1. Center MV. Available from: https://www.maastrichtuniversity.nl/about-um/units/maastricht-valorisation-centre. cited 2017.

2. Read J, Jones R, Owen G, Leavitt BR, Coleman A, Roos RA, et al. Quality of life in Huntington's disease: a comparative study investigating the impact for those with pre-manifest and early manifest disease, and their partners. Journal of Huntington's disease. 2013;2(2):159-75.